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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Treatment Resistance in Depression: Neuroimaging Biomarkers and Rare Variants

Liston *et al.* (pages 517–526) assessed the impact of left dorsolateral prefrontal transcranial magnetic stimulation (TMS) on functional connectivity in a longitudinal study of patients undergoing treatment for depression. TMS normalized depression-related hyperconnectivity between the subgenual cingulate and medial prefrontal areas of the default mode network, but did not alter connectivity in the central executive network. Individual differences in subgenual cingulate connectivity predicted subsequent treatment response. These findings indicate that TMS may act, in part, by selectively modulating network-level connectivity and highlight a potential neuroimaging biomarker for treatment response prediction.

Standard treatments for major depression often fail to lead to clinical recovery. In an attempt to identify a biomarker to predict such failure, **McGrath *et al.*** (pages 527–535) examined regional cerebral glucose metabolism using position emission tomography in patients with major depressive disorder (MDD) randomly assigned to receive either escitalopram or cognitive behavioral therapy. Compared with patients who achieved remission, nonresponders showed higher pretreatment metabolism in subcallosal cingulate and superior temporal sulcus, suggesting a distinct metabolic pattern.

No consistent genetic associations have yet been identified for antidepressant treatment response. **O'Dushlaine *et al.*** (pages 536–541) analyzed rare deletions and duplications for association with treatment resistance in MDD, using data from two cohorts. Their results suggest that duplications may be more common among individuals with treatment resistance, although no specific locus was strongly implicated and no findings survived correction.

Brain Stimulation Reward Deficits Induced By Social Defeat Stress

Social stress induces reward deficits, a key feature of depressive disorders, but the impact of social stress on brain reward function remains incompletely understood. Using intracranial self-stimulation, **Der-Avakian *et al.*** (pages 542–549) show that social stress produces profound and enduring brain reward deficits in susceptible, but not resilient, rats. Susceptibility was associated with increased mammalian target of rapamycin expression in the ventral tegmental area. Furthermore, reversal of brain reward deficits with chronic antidepressant treatment correlated with lower reward deficit severity.

Donahue *et al.* (pages 550–558) report that anhedonia-like behavior, as measured by intracranial self-stimulation, emerges in mice exposed to daily social defeat stress, an effect that was attenuated in mice that overexpress ΔFosB. Acute administration of ketamine had no effect on defeat-induced anhedonia, but reversed elevations in social avoidance. These findings indicate that social defeat reduces preference for rewards and suggests that not all depressive-like symptoms in this rodent model of depression are equally sensitive to acute ketamine.

Omega-3 Fatty Acids for Prevention of Interferon-α-Induced Depression

There is a high risk of depression in patients with increased inflammation, including those receiving cytokines for medical treatment. Omega-3 polyunsaturated fatty acids are nutritional compounds with antidepressant and anti-inflammatory action. In this randomized, double-blind, two-week study, **Su *et al.*** (pages 559–566) report that treatment with eicosapentaenoic acid (EPA), but not docosahexaenoic acid (DHA) or placebo, decreased the incidence of interferon-α-induced depression in patients being treated for hepatitis C. Both EPA and DHA delayed the onset of depression, suggesting that omega-3 fatty acids may be an effective strategy for the prevention of inflammation-associated depression.

Structural Connectome Alterations in Depression

Research suggests that MDD is associated with a disrupted topological organization of functional brain networks, but it is unclear whether these changes have a structural basis. **Korgaonkar *et al.*** (pages 567–574) used diffusion tensor imaging with network-based statistics and graph theory analyses to examine the structural alterations in brain pathways. They found two distinct brain networks, comprised of the default mode network and frontal-thalamo-caudate regions, with lowered structural connectivity in patients with MDD compared to control subjects.

Effects of Peripheral Inflammation: Depression and Impaired Cognition

Traumatic brain injury is associated with a higher incidence of depression. **Fenn *et al.*** (pages 575–584) report that traumatic brain injury in mice caused neuroinflammation, motor coordination deficits and depressive-like behavior that largely resolved within 7 days. However, they also found evidence of primed microglia, innate immune cells of the brain, 30 days post-injury. Following an acute inflammatory challenge, the primed microglia showed a hyperactive response that was associated with the onset of depressive-like behavior. These findings suggest that brain injury may increase the tendency to develop depression under conditions when the immune system is activated.

Animal studies have suggested that systemic inflammation impairs cognition and the medial temporal lobe. Using position emission tomography in healthy volunteers, **Harrison *et al.*** (pages 585–593) demonstrate that an inflammatory challenge acutely reduced medial temporal lobe glucose metabolism and compromised spatial, but not procedural, memory. These data suggest a mechanism to support epidemiological data linking inflammation to risk of age-related cognitive decline and progression of neurodegenerative disorders such as Alzheimer's disease.

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